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Chemoselective Carbozincation of Cyclopropene for C–C Bond Formation and Cleavage in a Single Operation

Kohei Endo,*[a,b] Takeo Nakano,[a] Shuhei Fujinami,[a] and Yutaka Ukaji[a]

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The carbozincation of cyclopropene and cleavage of cyclopropylzinc generates carbanion intermediates, which in turn can generate oligomeric complexes in situ through successive carbozincation reactions. The present reaction controls the carbozincation sequence and C–C bond cleavage to give densely functionalized and sterically congested alkylamines in a single operation. A subtle difference in the substituent at the C=N bond induced chemoselective carbozincation of cyclopropene.

Introduction

The cleavage of a single C–C bond without the use of transition metals could lead to innovative transformations in organic chemistry. The oxidative cleavage of a C–C bond by using transition metals has been widely developed, but the use of inexpensive and abundant main group metals for C–C bond cleavage still represents a formidable challenge.[1] The generation of strained organometallic intermediates would be promising as an initial step in the reconstruction of organic molecules without transition metals in a single operation. Although the use of cyclopropane as a motif for C–C bond cleavage is a conventional approach, the chemoselective ring opening of cyclopropane is difficult to control (Figure 1).[1,2] The typical approach used to prepare a precursor for C–C bond cleavage is the carbometalation of cyclopropene by using organometallic reagents; however, cyclopropylmetallic intermediates are generally stable enough for use in various cyclopropanation reactions even in the presence of transition-metal catalysts for cross-coupling reactions.[3] Furthermore, the conversion of a C–metal bond into a different C–metal bond through cleavage of a C–C bond in cyclopropane seems to be disadvantageous from the viewpoint of the thermodynamic stability of the organometallic intermediates.[4] The sequential carbometalation of cyclopropene with a cyclopropylmetal or allylmetal intermediate after C–C bond cleavage would lead to oligomeric products, as the products are also similarly reactive carbanion intermediates.[2] Thus, a reaction mixture would potentially include a variety of carbanion intermediates, such as carbanions **1** to ∞ in Figure 1, during C–C bond formation/cleavage. In situ generated carbanions **1** to ∞ would give various adducts with electrophiles, such as C=X bonds (Figure 2). The straightforward control of carbanion intermediates before and after C–C bond cleavage seems to be difficult to achieve; therefore, a gimmick, such as retroaldol-type C–C bond cleavage, is used to control the reactivity and to terminate further in situ reactions.[4] We have developed a wide variety of catalyzed and uncatalyzed carbometalation reactions of unsaturated C–C bonds.[5] Thus, we further pursue the control of the carbometalation and C–C bond cleavage sequence via carbanion intermediates for the reconstruction of densely functionalized molecules without the use of transition metals, even as catalysts. We first

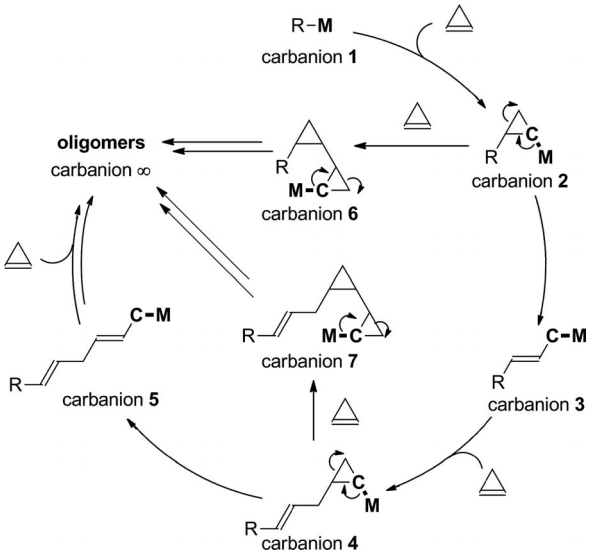

Figure 1. Catalyst-free generation of carbanion intermediates through carbometalation of cyclopropene.[2]

[a] Department of Chemistry, Graduate School of Natural Science and Technology, Kanazawa University,
Kakuma, Kanazawa, Ishikawa 920-1192, Japan
E-mail: kendo@se.kanazawa-u.ac.jp
http://chem.s.kanazawa-u.ac.jp/org/index.html
[b] PRESTO, Japan Science and Technology Agency (JST),
4-1-8 Honcho, Kawaguchi, Saitama 332-0012, Japan

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studied a C–C bond formation and cleavage sequence in situ through the chemoselective carbozincation of cyclopropene. During the course of our studies, we discovered that a subtle difference in the substituent in the reaction of the carbonyl derivatives, cyclopropene, and organozinc reagents dramatically changed the reaction pathway and achieved C–C bond formation by the carbozincation of cyclopropene, successive C–C bond cleavage of a cyclopropylzinc intermediate, and addition of the in situ generated organozinc intermediate to unactivated hydrazone in a single operation.[6] This paper describes C–C bond cleavage through the carbozincation of cyclopropene and tandem diastereoselective C–C bond formation to give densely functionalized and sterically congested products, which offers promise as a reconstruction approach to organic molecules without the need for transition-metal catalysts.

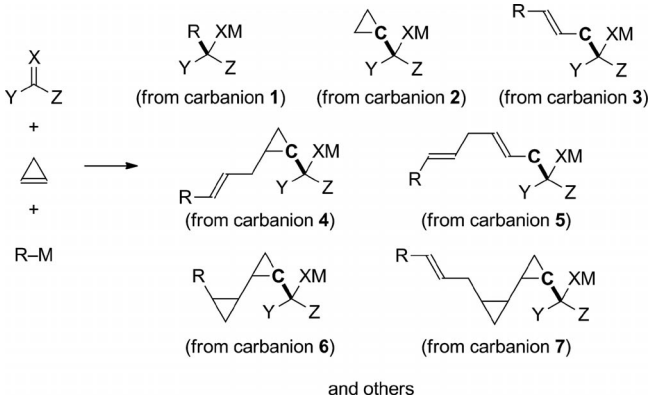
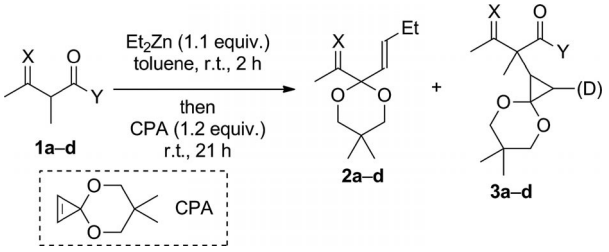


Figure 2. Addition of carbanions derived from cyclopropene to electrophile.

Results and Discussion

The results of the initial screening of substrates are presented in Table 1. The deprotonation of β-keto ester **1a** by using Et_2Zn and the subsequent addition to cyclopropenone acetal (CPA)[7] gave a complicated mixture (Table 1, entry 1). The reaction of imine **1b** derived from **1a** under the same reaction conditions also gave a complicated mixture (Table 1, entry 2). The reaction of imine **1c** derived from β-ketoamide and allylamine was carried out to give predominantly cyclopropylated product **3c** without C–C bond cleavage; the reaction quenched by using D_2O gave product **3c** with approximately 60% deuteration at the sp^3 carbon atom of cyclopropane (Table 1, entry 3). In sharp contrast, the reaction of hydrazone **1d** derived from β-ketoamide gave unexpected product **2d** in low yield (Table 1, entry 4).[8] Thus, the use of hydrazone seemed to be important in promoting an unexpected pathway. The subtle difference in the substituent at the C=N bond produced a dramatic change in the reaction pathway.

Table 1. Screening of substrates.

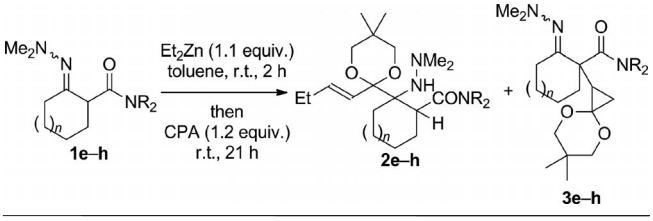


Entry	**1**, X	Y	Product, yield [%]
1	**1a**, O	OEt	complicated
2	**1b**, allyl-N	OEt	complicated
3	**1c**, allyl-N	NMe_2	**2c**, n.d.;[a] **3c**, 62[b]
4	**1d**, Me_2N–N	NMe_2	**2d**, 31; **3d**, n.d.[a]

[a] n.d.: not detected. [b] Single diastereomer was obtained. The geometry could not be determined.

Table 2 shows the effect of the cyclic hydrazone. Cyclohexanone derivative **1e** gave a nonisolable mixture of corresponding products **2e** and **3e**; cyclic substrates gave the corresponding sterically congested product **2e** through allylation of the hydrazone moiety, which generally seems to be sluggish (Table 2, entry 1).[9,10] The cyclohexanone derivative bearing a diethylamide moiety improved the yield and selectivity; product **2f** was obtained as a single diastereomer and a small amount of **3f** was obtained (Table 2, entry 2). The reaction of cyclopentanone derivative **1g** gave unidentified products (Table 2, entry 3). Cycloheptanone derivative **1h** gave a complicated mixture (Table 2, entry 4). Therefore, cyclohexanone derivatives bearing a diethylamide group were chosen as initial substrates.

Table 2. Effect of cyclic substrates.



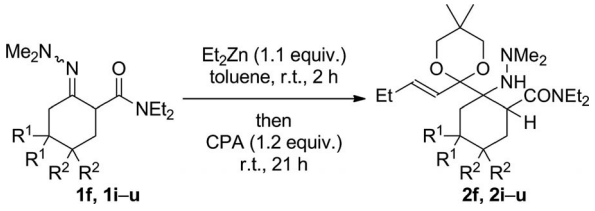
Entry	**1**, *n*	R	Product, yield [%]
1	**1e**, 1	Me	**2e**, 40;[a] **3e**, 20[a]
2[b]	**1f**, 1	Et	**2f**, 69;[c] **3f**, 8
3	**1g**, 0	Et	unidentified products
4	**1h**, 2	Et	complicated

[a] Yield was determined by NMR spectroscopy as a result of the inseparable mixture. [b] The corresponding β-ketoamide did not give the product. [c] Single diastereomer was obtained.

We focused on the unprecedented reaction by using hydrazone derivatives **1f** and **1i**–**u** and CPA to obtain densely functionalized and sterically congested cyclohexylamines **2f** and **2i**–**u** as single diastereomers, respectively (Table 3).[11] The reaction proceeded even at room temperature, and the low conversion gave low yields of products **2**. Only hydrazone **1f** gave cyclopropylated product **3f** in low yield as a byproduct, and generally hydrazones **1i**–**u** bearing

substituents did not give cyclopropylated products **3i**–**u** at all. A simple substituent at the 4-position of the cyclohexane moiety did not affect the yields of the products; products **2f** and **2i**–**m** were obtained in yields of 60–72% (Table 3, entries 1–6). In contrast, heteroatom substituents slowed the reaction rate; benzyl ether **1n** gave desired product **2n** in 28% yield (Table 3, entry 7). These low yields were attributed to the low conversion of the substrates. The use of dimethylated **1o** gave desired product **2o** in 82% yield (Table 3, entry 8). The reaction of dioxolane **1p** gave desired product **2p** in moderate yield; low conversion was observed (Table 3, entry 9). The incorporation of an exo methylene moiety in **1q** diminished the yield of product **2q** (Table 3, entry 10). The use of **1r**, **1s**, and **1t** gave desired products **2r**, **2s**, and **2t** (Table 3, entries 11–13). In contrast, the reaction of **1u** did not give the desired product; 1,3-diaxial repulsion seems to inhibit the allylation reaction (Table 3, entry 14). A fine single crystal was obtained from product **2r**, and its relative configuration was ascertained by single-crystal X-ray analysis. As NOESY analysis of products **2f**–**t** did not show the exact correlation, we deduced the relative configurations of other products by the comparison of the NMR spectra.

Table 3. Effect of cyclic substrates.



1f, 1i–u **2f, 2i–u**

Entry	Hydrazone	Product, yield [%][a]
1	**1f**, $R^1 = R^2 = H$	**2f**, 69 (20)[b]
2	**1i**, $R^1 = H$; R^2, R^2 = Me, H	**2i**, 60
3	**1j**, $R^1 = H$; R^2, R^2 = *n*-C_3H_7, H	**2j**, 63
4	**1k**, $R^1 = H$; R^2, R^2 = *n*-C_5H_{11}, H	**2k**, 71
5	**1l**, $R^1 = H$; R^2, R^2 = *t*Bu, H	**2l**, 72
6	**1m**, $R^1 = H$; R^2, R^2 = Ph, H	**2m**, 66
7	**1n**, $R^1 = H$; R^2, R^2 = OBn, H	**2n**, 28
8	**1o**, $R^1 = H$; R^2, R^2 = Me, Me	**2o**, 82
9	**1p**, $R^1 = H$; R^2, R^2 = –O(CH_2)$_2$O–	**2p**, 40
10	**1q**, $R^1 = H$, R^2, R^2 = CH_2	**2q**, 26
11	**1r**, R^1, R^1 = Me, H; $R^2 = H$	**2r**, 73[c]
12	**1s**, R^1, R^1 = Ph, H; $R^2 = H$	**2s**, 59
13	**1t**, R^1, R^1 = 4-BrC_6H_4, H; $R^2 = H$	**2t**, 31
14	**1u**, R^1, R^1 = Me, Me; $R^2 = H$	**2u**, trace

[a] A single diastereomer was obtained in each case. [b] Me_2Zn was used instead of Et_2Zn. [c] Single-crystal X-ray structure analysis.

The proposed mechanism is shown in Figure 3. The use of ketimine derivative **A-II** after deprotonation leads to C–C bond formation at the α-carbon to give Prod-**III** (carbanion **iv**). The deprotonation reaction or coordination of hydrazone gives Zn intermediate **A-I**, and subsequent carbozincation of cyclopropene in CPA gives cyclopropylzinc intermediate **B** (carbanion **i**).[4,5,12] Subsequent C–C bond cleavage of **B** gives allylzinc intermediate **C** (carbanion **ii**) or **D** (carbanion **iii**).[2,13] The intramolecular coordination of an oxygen atom of the acetal moiety on the Zn center might stabilize allylzinc intermediate **C** or **D**, which would inhibit further carbozincation of cyclopropene. The nucleophilic addition to an unactivated hydrazone moiety in allylzinc intermediate **D** gives Zn intermediate **E**.[14] However, at this point we cannot exclude the possibility of intermolecular allylation.[15,16] The reactivities of Et_2Zn, **B** (carbanion **i**), **C** (carbanion **ii**), and **D** (carbanion **iii**) could be controlled without competitive oligomerization, as described in Figure 1. An acyclic substrate, such as **1d**, promotes a retro-Mannich-type reaction to give Prod-**II**, and a cyclic substrate, such as **1f** and **1i**–**t**, hampers the retro-Mannich-type reaction to give Prod-**I**. Although some of the steps are still unclear, the present pathway seems to be reasonable. The diastereoselectivity could be derived from the relative configuration of the allylic and amide moieties at the equatorial positions (Figure 4). The deprotonation pathway induces diastereoselective protonation; steric hindrance around the dimethylamino group would inhibit equatorial protonation.[17,18]

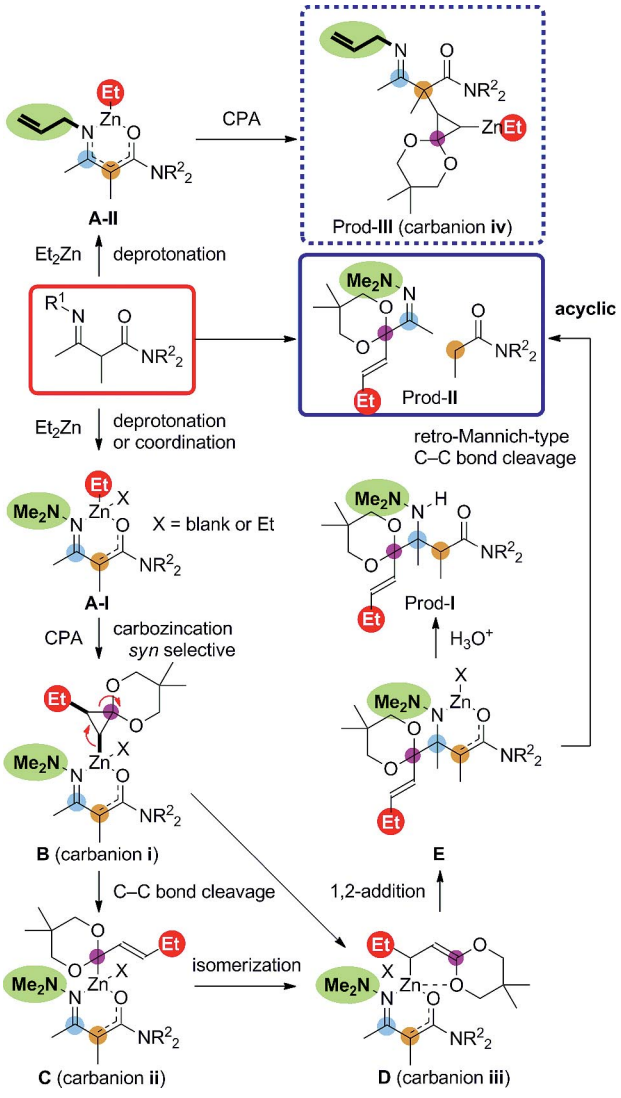


Figure 3. Proposed mechanism.

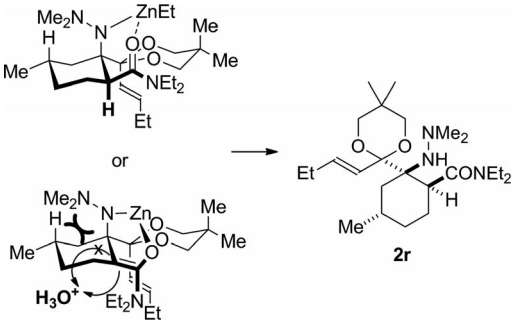
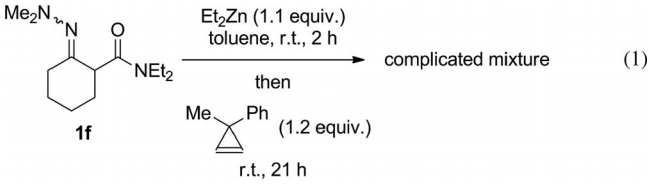
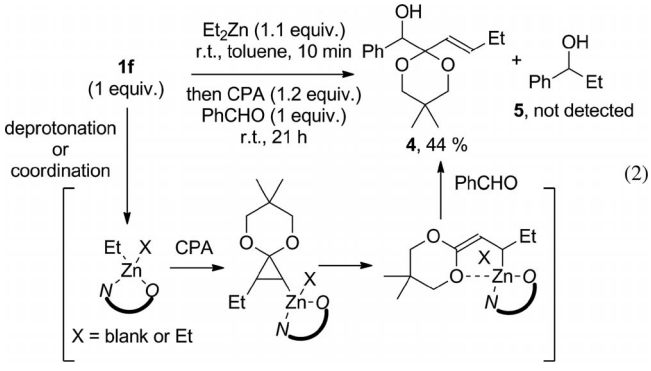


Figure 4. Model for diastereoselectivity of **2r**.

We tentatively examined the use of a simple cyclopropene, that is, (1-methyl-2-cyclopropenyl)benzene, in the present reaction [Eq. (1)]. Similar reaction conditions promoted the reaction of **1f**, which was consumed completely, but unidentified complicated products were obtained. The suppression of uncontrollable carbanion intermediates, such as those in Figure 1, seems to be a key for chemoselective C–C bond formation and cleavage.



The intermolecular allylation reaction through the carbozincation of CPA was tentatively examined.[19] To our delight, the reaction of **1f**, Et_2Zn (1.1 equiv.), and CPA (1.2 equiv.), followed by the addition of benzaldehyde gave product **4** [Eq. (2)]. Accordingly, hydrazone **1f** could act as a ligand for the carbozincation of cyclopropene and C–C bond cleavage to give an allylzinc intermediate, which achieved the formal intermolecular addition of an α,β-unsaturated acyl anion equivalent to benzaldehyde.[20] Typical product **5** was not obtained at all with the use of Et_2Zn. The synthetic utility of the present α,β-unsaturated acyl anion equivalent with the use of simple ligands will be developed further.



Conclusions

We achieved chemoselective C–C bond cleavage of cyclopropylzinc as a model for the development of a reconstruction strategy of organic molecules by using inexpensive and abundant main group metals in a single operation. The chemoselective carbozincation of cyclopropene, subsequent C–C bond cleavage of cyclopropylzinc, and allylation of an unactivated hydrazone proceeded to give densely functionalized and sterically congested cyclohexylamines as single diastereomers. Successive carbozincation of cyclopropene/C–C bond cleavage for the generation of carbanion intermediates, leading to oligomers, could be controlled through the present approach. The allylzincation of various electrophiles by using cyclopropene will be examined further. Chemoselective C–C bond cleavage through the carbozincation of unstrained molecules, and its synthetic applications, are currently being studied in our laboratory.

CCDC-955495 (for **2r**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): General procedures, physical properties of all new compounds, and NMR spectra of new compounds.

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[17] The reaction of **1f** and Et_2Zn for 10 min, and the subsequent addition of CPA gave 64% yield of product **2f** and 8% yield of **3f**; see also ref.[9]

[18] The diastereoselectivity was similar to that obtained in the reaction of an allylzinc halide and a β-ketoamide; see ref.[15]

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